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(74) Agent: BOONE, Jeffrey, S.; 675 McDonnell Boulevard,
P.O. Box 5840, St. Louis, MO 63134 (US).

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09/898,885 3 July 2001 (03.07.2001) US(71) Applicant (for all designated States except US):
MALLINCKRODT, INC. [US/US]; 675 McDonnell
Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RAJAGOPALAN,
Raghavan [US/US]; Gliatech, 23420 Commerce Park
Road, Beechwood, OH 44122 (US). ACHILEFU, Samuel,
I. [NG/US]; 3424 San Sevilla Court, St. Louis, MO 63044
(US). BUGAJ, Joseph, E. [US/US]; 2916 Kettering Drive,
St. Charles, MO 63303 (US). DORSHOW, Richard,
B. [US/US]; 11977 Neihaus Lane, St. Louis, MO 63146
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(54) Title: DYE-AZIDE COMPOUNDS FOR DUAL PHOTOTHERAPY

(57) Abstract: The present invention discloses dye-azide derivatives and their bioconjugates for dual phototherapy of tumors and
other lesions. The compounds of the present invention may contain either a mixture of Type 1 and Type 2 agents or a single entity
that integrates both units in the same molecules. The compounds are designed to produce both Type 1 and Type 2 phototherapeutic
effect at once using dual wavelength light source that will produce singlet oxygen and nitrene at the lesion of interest.

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DYE-AZIDE COMPOUNDS FOR DUAL PHOTOTHERAPY**FIELD OF THE INVENTION**

The present invention relates generally to novel compounds useful for dual phototherapeutic procedures and particularly to phototherapeutic procedures using dye-azide compounds.

5 BACKGROUND OF THE INVENTION

The use of visible and near-infrared (NIR) light in clinical practice is growing rapidly. Compounds absorbing or emitting in the visible or NIR, or long-wavelength (UV-A, > 350 nm) region of the electromagnetic spectrum are potentially useful for optical tomographic imaging, endoscopic visualization, and
10 phototherapy. However, a major advantage of biomedical optics lies in its therapeutic potential. Phototherapy has been demonstrated to be a safe and effective procedure for the treatment of various surface lesions, both external and internal. Its efficacy is akin to radiotherapy, but it advantageously lacks the harmful radiotoxicity to critical non-target organs.

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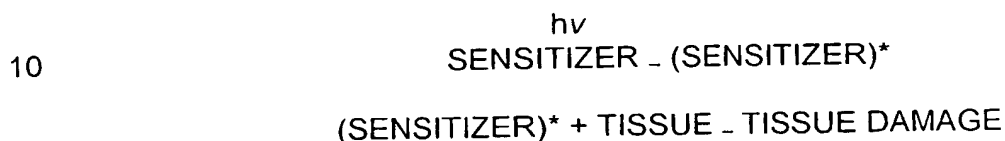
Phototherapy has been in existence for many centuries and has been used to treat various skin surface ailments. As early as 1400 B.C. in India, plant extracts (psoralens), in combination with sunlight, were used to treat vitiligo. In 1903, Von Tappeiner and Jesionek, used eosin as a photosensitizer for treating skin cancer, lupus of the skin, and condylomata of female genitalia. Over the years, the combination of psoralens and ultraviolet A (low-energy) radiation has been used to treat a wide variety of dermatological diseases and manifestations including psoriasis, parapsoriasis, cutaneous T-cell lymphoma, eczema, vitiligo, areata, and neonatal bilirubinemia. Although the potential of cancer phototherapy has been recognized since the early 1900's, systematic studies to demonstrate safety and efficacy began only in 1967 with the treatment of breast carcinoma. In 1975, Dougherty et al. conclusively established that long-term cure is possible with photodynamic therapy (PDT). Currently, phototherapeutic methods are also being investigated for the treatment of some cardiovascular disorders such as atherosclerosis and vascular restenosis, for the treatment of rheumatoid arthritis, and for the treatment of some inflammatory diseases such as Chron's disease.

Phototherapeutic procedures require photosensitizers (i.e. chromophores) having high absorptivity. These compounds should preferably be chemically inert, and become activated only upon irradiation with light of an appropriate wavelength. Selective tissue injury can be induced with light when photosensitizers bind to the target tissues, either directly or through attachment to a bioactive carrier. Furthermore, if the photosensitizer is also a chemotherapeutic agent (e.g., anthracycline antitumor agents), then an enhanced therapeutic effect can be attained. The key requirements for the design of effective phototherapeutic agents are: (a) large molar extinction coefficients, (b) long triplet lifetimes, (c) high

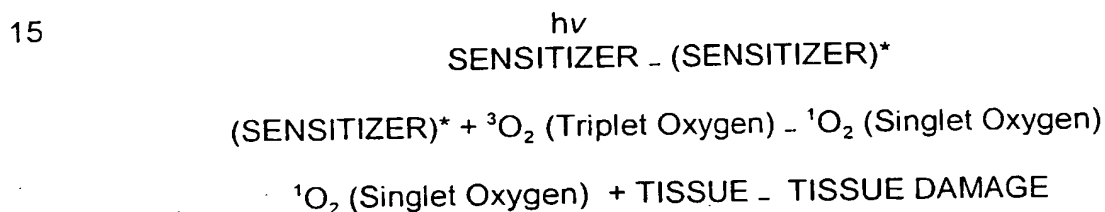
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yields of singlet oxygen and/or other reactive intermediates, viz., free radicals, nitrenes, carbenes, or open-shell ionic species such as carbonium ions and the like, (d) efficient energy or electron transfer to cellular components, (e) low tendency to form aggregation in an aqueous milieu, (f) efficient and selective
 5 targeting of lesions, (g) rapid clearance from the blood and non-target tissues, (h) low systemic toxicity, and (i) lack of mutagenicity.

Photosensitizers operate via two distinct mechanisms, termed Types 1 and 2. The type 1 mechanism is shown in the following scheme:



Type 1 mechanisms involve direct energy or electron transfer from the photosensitizer to the cellular components thereby causing cell death. Type 2 mechanisms involve two distinct steps, as shown in the following scheme:



In the first step, singlet oxygen is generated by energy transfer from the triplet
 20 excited state of the photosensitizer to the oxygen molecules surrounding the tissues. In the second step, collision of singlet oxygen with the tissues promotes tissue damage. In both Type 1 and Type 2 mechanisms, the photoreaction proceeds via the lowest triplet state of the sensitizer. Hence, a relatively long triplet lifetime is required for effective phototherapy. In contrast, a relatively short

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triplet lifetime is required to avoid photodamage to the tissue caused by photosensitizers.

The biological basis of tissue injury brought about by tumor phototherapeutic agents has been the subject of intensive study. Various biochemical mechanisms for tissue damage have been postulated even though the type and number of photosensitizers employed in these studies are relatively small. These biochemical mechanisms are as follows: a) cancer cells upregulate the expression of low density lipoprotein (LDL) receptors, and photodynamic therapy (PDT) agents bind to LDL and albumin selectively; (b) porphyrin-like substances are selectively taken up by proliferative neovasculature; (c) tumors often contain increased number of lipid bodies and are thus able to bind to hydrophobic photosensitizers; (d) a combination of "leaky" tumor vasculature and reduced lymphatic drainage causes porphyrin accumulation; (e) tumor cells may have increased capabilities for phagocytosis or pinocytosis of porphyrin aggregates; (f) tumor associated macrophages may be largely responsible for the concentration of photosensitizers in tumors; and (g) cancer cells may undergo apoptosis induced by photosensitizers. Among these mechanisms, (f) and (g) are the most general and, of these two alternatives, there is a general consensus that (f) is the most likely mechanism by which the phototherapeutic effect of porphyrin-like compounds is induced.

Most of the currently known photosensitizers are commonly referred to as photodynamic therapy (PDT) agents and operate via the Type 2 mechanism. For example, Photofrin II (a hematoporphyrin derivative) has been recently approved by the United States Food and Drug Administration for the treatment of bladder, esophageal, and late-stage lung cancers. However, Photofrin II has been

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shown to have several drawbacks: a low molar absorptivity ($\epsilon = 3000 \text{ M}^{-1}$), a low singlet oxygen quantum yield ($\Phi = 0.1$), chemical heterogeneity, aggregation, and prolonged cutaneous photosensitivity. Hence, there has been considerable effort in developing safer and more effective photosensitizers for PDT which exhibit

5 improved light absorbance properties, better clearance, and decreased skin photosensitivity compared to Photofrin II. These include monomeric porphyrin derivatives, corrins, cyanines, phthalocyanines, phenothiazines, rhodamines, hypocrellins, and the like. However, these phototherapeutic agents also mainly operate via the Type 2 mechanism.

10 Surprisingly, there has not been much attention directed at developing Type 1 phototherapeutic agents, despite the fact that the Type 1 mechanism appears to be inherently more efficient than the Type 2 mechanism. First, unlike Type 2, Type 1 photosensitizers do not require oxygen for causing cellular injury. Second, the Type 1 mechanism involves two steps (photoexcitation

15 and direct energy transfer), whereas the Type 2 mechanism involves three steps (photoexcitation, singlet oxygen generation, and energy transfer). Furthermore, certain tumors have hypoxic regions, which renders the Type 2 mechanism ineffective. However, in spite of the drawbacks associated with the Type 2 mechanism, only a small number of compounds have been developed that

20 operate through the Type 1 mechanism, e.g. anthracycline antitumor agents.

Thus, there is a need to develop effective phototherapeutic agents. Phototherapeutic efficacy can be substantially improved if both Type 1 and Type 2 units are integrated into a single composition. This can be accomplished using three types of formulation: (a) homogeneous mixtures of Type 1 or Type 2 agents

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alone, (b) heterogeneous mixtures of Type 1 and Type 2 agents, or (c) a single molecular entity containing both Type 1 and Type 2 functionalities.

SUMMARY OF THE INVENTION

The present invention discloses novel compounds including organic azides for phototherapy of tumors and other lesions. More specifically, the present invention discloses compounds having the formula



wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes. E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules. L is selected from the group consisting of $-(\text{CH}_2)_a-$, $-(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{OCONH}-$, $-\text{OCO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, $-\text{HNNHCO}-$, $-\text{OSO}_2-$, $-\text{NR}^3(\text{CH}_2)_e\text{CONR}^4-$, $-\text{CONR}^5(\text{CH}_2)_f\text{NR}^6\text{CO}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$. X is either a single bond or is selected from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-\text{HNCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$. R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, $-\text{OH}$, C1-C10 polyhydroxyalkyl, C1-C10 alkoxy, C1-C10 alkoxyalkyl, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$. R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl,

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C5-C10 aryl, and C1-C10 polyhydroxyalkyl. And a to l independently range from 0 to 10.

The present invention also discloses a method of performing a therapeutic procedure using the compounds of the present invention. An effective amount of organic azide photosensitizer having the formula



is administered to a subject. In this formula, DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes. E is a hydrogen atom or is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules. L is selected from the group consisting of $-(\text{CH}_2)_a-$, $-(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{OCONH}-$, $-\text{OCO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, $-\text{HNNHCO}-$, $-\text{OSO}_2-$, $-\text{NR}^3(\text{CH}_2)_e\text{CONR}^4-$, $-\text{CONR}^5(\text{CH}_2)_f\text{NR}^6\text{CO}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$. X is either a single bond or is selected from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-\text{HNCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$. R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, $-\text{OH}$, C1-C10 polyhydroxyalkyl, C1-C10 alkoxy, C1-C10 alkoxyalkyl, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$. R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl. And a to l independently range from

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0 to 10. Following administration, the photosensitizer is allowed to accumulate in target tissue which is exposed to a light of wavelength between 300 and 950 nm. This light has sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

5 In an alternative embodiment of the method of the present invention, the compounds of the present invention may be used to perform a phototherapeutic procedure including the following steps. A homogeneous photosensitizing mixture consisting of two or more Type 1 agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is
10 exposed to a light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the target tissue.

 In another alternative embodiment of the method of the present invention, the compounds of the present invention may be used to perform a phototherapeutic procedure including the following steps. A homogeneous
15 photosensitizing mixture consisting of two or more Type 2 (PDT) agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the target tissue.

 In a further alternative embodiment of the method of the present
20 invention, the compounds of the present invention may be used to perform a phototherapeutic procedure including the following steps. A heterogeneous photosensitizing mixture consisting of one or more Type 1 agents and one or more Type 2 agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to light of wavelength between 300 and 950 nm

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with sufficient power and fluence rate to cause necrosis or apoptosis of said target tissue.

These and other advantages and embodiments of the inventive compounds and methods will be apparent in view of the following Figures, description, and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic mechanism for activation of the inventive compounds;

Fig. 2 is a schematic mechanism for the synthesis of a phthalocyanine derivative; and

Fig. 3 is a schematic mechanism for the synthesis of a cyanine derivative.

DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses dye-azide derivatives and their bioconjugates for phototherapy of tumors and other lesions. The compounds have the general formula,



wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, indolenium dyes, and the like; E is either a hydrogen atom or is selected from the group comprising antibodies, peptides, peptidomimetics, carbohydrates,

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glycomimetics, drugs, hormones, or nucleic acids; L is a linker unit selected from the group comprising $-(CH_2)_a-$, $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-OCONH-$, $-OCO_2-$, $-HNCONH-$, $-HNCSNH-$, $-HNNHCO-$, $-OSO_2-$, $-NR^3(CH_2)_eCONR^4-$, $-CONR^5(CH_2)_fNR^6CO-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either

5 a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-CO-$, $-OCO-$, $-HNCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, $-OH$, C1-C10 polyhydroxyalkyl, C1-C10 alkoxyl, C1-C10 alkoxyalkyl, $-SO_3H$, $-(CH_2)_kCO_2H$, or $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10

10 alkyl, C5-C10 aryl, or C1-C10 polyhydroxyalkyl; and a to l independently range from 0 to 10.

In one embodiment, azides according to the present invention have the general formula 1 above wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines,

15 phthalocyanines, rhodamines, phenothiazines, fluoresceins, porphyrins, benzoporphyrins, and corrins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin (ST) receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin (CCK) receptor binding molecules,

20 steroid receptor binding molecules, and carbohydrate receptor binding molecules; L is selected from the group consisting of $-HNCO-$, $-CONR^1-$, $-HNCONH-$, $-HNCSNH-$, $-HNNHCO-$, $-(CH_2)_aCONR^1-$, $-CONR^1(CH_2)_aNR^2CO-$, and $-NR^1CO(CH_2)_aCONR^2-$; R^1 and R^2 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl; and a, b, and c

25 independently range from 0 to 6.

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In an alternative embodiment, azides according to the present invention have the general formula 1 above wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, phthalocyanines, rhodamines, porphyrins, benzoporphyrins, and corrins; E is a
5 selected from the group consisting of octreotide and octreotate peptides, heat-sensitive bacterioendotoxin receptor binding peptides, carcinoembryonic antigen antibody (anti-CEA), bombesin receptor binding peptide, neurotensin receptor binding peptide, cholecystekinin receptor binding peptide, and estrogen steroids; L is selected from the group consisting of -HNCO-, -CONR¹-, -HNCSNH-, -
10 HNNHCO-, -(CH₂)_aCONR¹-, -CONR¹(CH₂)_aNR²CO-, and R¹ and R² are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C5 polyhydroxyalkyl; and a, b, and c independently range from 0 to 6.

These compounds operate by a dual mechanism as shown in Fig. 1. N₃ is the azide moiety that produces nitrene upon photoactivation and DYE is
15 an aromatic chromophore that undergoes photosensitization and produces singlet oxygen for PDT. Aliphatic azido compounds can also be used for phototherapy, but may require high-energy light for activation unless the azide moiety is attached to conjugated polyene system. L is a linker between the chromophore and the epitope. Epitope (E) is a particular region of the molecule that is recognized by,
20 and binds to, the target site on the cell. An epitope is usually, but not always, associated with biomolecules, which includes hormones, amino acids, peptides, peptidomimetics, proteins, nucleosides, nucleotides, nucleic acids, enzymes, carbohydrates, glycomimetics, lipids, albumins, mono- and polyclonal antibodies, receptors, inclusion compounds such as cyclodextrins, and receptor binding
25 molecules. Specific examples of biomolecules include steroid hormones for the

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treatment of breast and prostate lesions, somatostatin, bombesin, and neurotensin receptor binding molecules for the treatment of neuroendocrine tumors, cholecystekinin (CCK) receptor binding molecules for the treatment of lung cancer, heat sensitive bacterioendotoxin (ST) receptor and carcinoembryonic antigen (CEA) binding molecules for the treatment of colorectal cancer, dihydroxyindolecarboxylic acid and other melanin producing biosynthetic intermediates for melanoma, integrin receptor and atheroscleratic plaque binding molecules for the treatment of vascular diseases, and amyloid plaque binding molecules for the treatment of brain lesions. Biomolecules for use in the present invention may also include synthetic polymers. Examples of synthetic polymers include polyaminoacids, polyols, polyamines, polyacids, oligonucleotides, aborols, dendrimers, and aptamers. Coupling of diagnostic and radiotherapeutic agents to biomolecules can be accomplished by methods well known in the art, as disclosed in Hnatowich et al., *Radioactive Labeling of Antibody: A simple and efficient method*. Science, 1983, 220, 613-615; A. Pelegri et al., *Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies*. Journal of Cellular Pharmacology, 1992, 3, 141-145; and U.S. Patent No. 5,714,342, each of which is expressly incorporated by reference herein in its entirety. Successful specific targeting of fluorescent dyes to tumors using antibodies and peptides for diagnostic imaging of tumors has been demonstrated by us and others, for example, in S.A. Achilefu et al., *Novel receptor-targeted fluorescent contrast agents for in vivo tumor imaging*, *Investigative Radiology*, 2000, 35(8), 479-485; B. Ballou et al., *Tumor labeling in vivo using cyanine-conjugated monoclonal antibodies*. Cancer Immunology and Immunotherapy, 1995, 41, 257-263; and K. Licha et al., *New contrast agents for optical imaging:*

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acid-cleavable conjugates of cyanine dyes with biomolecules. In Biomedical Imaging: Reporters, Dyes, and Instrumentation, D.J. Bornhop, C. Contag, and E.M. Sevick-Muraca (Eds.), Proceedings of SPIE, 1999, 3600, 29-35, each of which is expressly incorporated by reference herein in its entirety. Therefore, the

5 inventive receptor-targeted phototherapeutic agents are expected to be effective in the treatment of various lesions.

In the present invention, dual phototherapeutic effect involving both Type 1 and Type 2 mechanisms can be accomplished by incorporating the reactive intermediate precursors into a conventional PDT dyes and using a dual

10 wavelength light source to effect the generation of reactive intermediates as well as the generation of singlet oxygen. In some cases it may be possible to activate both Type 1 and Type 2 mechanisms using same wavelength of light. Dyes containing azide group have been prepared previously, as in S. Sunthankar et al., *Reactive disperse dyes. 1. Reactivity involving nitrene intermediate from azido*

15 *group.* Indian Journal of Chemistry, 1973, 11(5), 503-504, which is expressly incorporated by reference herein in its entirety.

In the process outlined in Fig. 1, the photoexcitation of the aromatic chromophore effects rapid intramolecular energy transfer to the azido group, resulting in bond rupture and production of nitrene and molecular nitrogen. The

20 nitrogen that is released is in vibrationally excited state, which may cause additional cellular injury.

For targeting purposes, external attachment of an epitope is used. If the aromatic azido compounds themselves preferentially accumulate in the target tissue, however, an additional binding group may not be needed. For

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example, if Ar is an anthracycline moiety, it will bind to cancer cells directly and would not require an epitope for targeting purposes.

The dye-azide derivatives of the present invention contain additional functionalities that can be used to attach various types of biomolecules, synthetic
5 polymers, and organized aggregates for selective delivery to various organs or tissues of interest. The synthesis of typical dual phototherapeutic agents incorporating both Type 1 and Type 2 mechanisms based on phthalocyanine and cyanine derivatives are shown in Figs. 2 and 3 respectively. Referring to Fig. 2, the diacid 1 can be prepared by the method analogous to phthalocyanine itself
10 described previously in J.E. van Lier and J.D. Spikes, *The chemistry, photophysics, and photosensitizing properties of phthalocyanines*, In Photosensitizing Compounds: Their Chemistry, Biology, and Clinical Use (Ciba Foundation Symposium 146), G. Bock and S. Harnett (Eds.), J. Wiley & Sons, 1989, pp. 17-32, which is expressly incorporated by reference herein its entirety.
15 The diacid 1 can be converted to the corresponding bis active ester in which one of the active esters can be condensed with an azide (by the Type 1 moiety) and the other active ester can be condensed with a biomolecule of interest to yield the phthalocyanine derivative 2. Referring to Fig. 3, the cyanine dye 3 is prepared by the alkylation of 2-methylbenzothiazole with N-succinimydyl bromoacetate followed
20 by condensation with malonaldehyde tetramethyl acetal. One of the active esters in the cyanine dye 3 can be attached to a Type 1 moiety and the other ester can be attached to a biomolecule to give the dual phototherapeutic agent 4. Specifically, the biomolecules bind to colorectal, cervical, ovarian, lung, and neuroendocrine tumors, and include somatostatin, cholecystekinin, bombesin,
25 neuroendocrine, and heat sensitive bacterioendotoxin receptor binding

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compounds. The other active ester can be conjugated to an aromatic or an aliphatic azides depending on the wavelength desired for excitation.

The novel compounds of the present invention may vary widely depending on the contemplated application. For tumors, the biomolecule is selected from the class of tumor markers including, but not limited to, 5 somatostatin, bombesin, neurotensin, cholecystekinin, heat sensitive bacterioendotoxin, estrogen, and progesterone receptor binding compounds. For vascular lesions, the biomolecule may be selected from the class of integrins, selectins, vascular endothelial growth factor, fibrins, tissue plasminogen activator, 10 thrombin, LDL, HDL, Sialyl Lewis^x and its mimics, and atherosclerotic plaque binding compounds.

Methods of performing therapeutic procedures with the inventive compound are also disclosed. An effective amount of the inventive compound in a pharmaceutically acceptable formulation is administered to a patient. For 15 example, parenteral administration advantageously contains a sterile aqueous solution or suspension of the photosensitizer in a concentration ranging from about 1 nM to about 0.5 M. Preferred parenteral formulations have a concentration of 1 μ M to 10 mM photosensitizer. Such solutions also may contain pharmaceutically acceptable buffers, emulsifiers, surfactants, and, optionally, electrolytes such as 20 sodium chloride. Formulations for enteral administration may vary widely, as is well known in the art. In general, such formulations are liquids, which include an effective amount of the complexes in aqueous solution or suspension. Such enteral formulations may optionally include buffers, surfactants, emulsifiers, thixotropic agents, and the like. Compounds for oral administration may also 25 contain flavoring agents and other ingredients for enhancing their organoleptic

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qualities. Formulations for topical delivery may also contain liquid or semisolid excipients to assist in the penetration of the photosensitizer. The compounds may also be delivered in an aerosol spray. The dose of the photosensitizer may vary from 0.1 to 500 mg/kg body weight, preferably from 0.5 to 2 mg/kg body weight.

5 The photosensitizer is allowed to accumulate in the region of interest, followed by illumination with the light of wavelength 300 to 1200 nm, preferably 350 to 850 nm, at the site of the lesion. If the lesion is on the skin surface, the photosensitizer can be directly illuminated; otherwise, endoscopic catheters equipped with a light source may be employed to achieve phototherapeutic effect. The intensity, power, 10 duration of illumination, and the wavelength of the light may vary widely depending on the location and site of the lesions. The fluence rate is preferably, but not always, kept below 200 mW/cm² to minimize thermal effects. Appropriate power depends on the size, depth, and the pathology of the lesion. The inventive compounds have broad clinical utility which includes, but is not limited to, 15 phototherapy of tumors, inflammatory processes, and impaired vasculature.

The inventive compounds can be formulated into diagnostic or therapeutic compounds for enteral, parenteral, topical, or cutaneous administration. Topical or cutaneous delivery of the photosensitizer may also include aerosol formulation, creams, gels, solutions, etc. The compounds are 20 administered in doses effective to achieve the desired diagnostic or therapeutic effect. Such doses may vary widely depending upon the particular complex employed, the organs or tissues to be examined, the equipment employed in the clinical procedure, the efficacy of the treatment achieved, and the like. These compounds contain an effective amount of the phototherapeutic agent, along with 25 conventional pharmaceutical carriers and excipients appropriate for the type of

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administration contemplated. These compounds may also include stabilizing agents and skin penetration enhancing agents.

The following example illustrates a specific embodiment of the invention pertaining to the preparation and properties of a typical bioconjugate
5 derived from bombesin, a bioactive peptide; 4-azido-2,3,5,6-tetrafluorophenylbenzoyl hydrazide, a Type I chromophore; and carboxymethylcyanine dye, a PDT chromophore. The above-listed compounds are well known to those skilled in the art and general descriptions of the compounds and their synthesis are described in U.S. Patent No. 6,180,085; Jori,
10 G., *Far-red-absorbing photosensitizers: their use in the photodynamic therapy of tumours*, J. Photochem. Photobiol. A: Chem., 62, (1992), 371-378; Patonay, G. and M. Antoine, *Near-Infrared Fluorogenic Labels: New Approach to an Old Problem*, Anal. Chem., 63:6, (1991) 321A-327A; and Jori, G. and E. Reddi, *Second Generation Photosensitizers for the Photodynamic Therapy of Tumours*,
15 in Light in Biology and Medicine, Volume 2 (ed. R.H. Douglas et al.), Plenum Press, New York, (1991), 253-266, the disclosures of which are herein incorporated by reference in their entireties.

As would be apparent to skilled artisans, various changes and modifications are possible and are contemplated within the scope of the invention
20 described. It should be understood that the embodiments of the present invention shown and described in the specification are only specific embodiments of the inventors, who are skilled in the art, and are not limiting in any way. Therefore, various changes, modifications or alterations to those embodiments may be made or resorted to without departing from the spirit of the invention and the scope of the
25 following claims. For example, although the compounds of the present invention

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are primarily directed at therapy, most of the compounds containing polycyclic aromatic chromophores can also be used for optical diagnostic imaging purposes.

What is claimed is:

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1. A compound comprising organic azides having the general formula



wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes; E is a hydrogen atom or is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules; L is selected from the group consisting of $-(\text{CH}_2)_a-$, $-(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{OCONH}-$, $-\text{OCO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, $-\text{HNNHCO}-$, $-\text{OSO}_2-$, $-\text{NR}^3(\text{CH}_2)_e\text{CONR}^4-$, $-\text{CONR}^5(\text{CH}_2)_f\text{NR}^6\text{CO}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-\text{HNCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, $-\text{OH}$, C1-C10 polyhydroxyalkyl, C1-C10 alkoxyl, C1-C10 alkoxyalkyl, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl; and a to l independently range from 0 to 10.

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2. The compound of claim 1 wherein DYE is an aromatic or a heteroaromatic radical derived from cyanines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
5 $(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 ,
10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

3. The compound of claim 1 wherein DYE is an aromatic or a heteroaromatic radical derived from phthalocyanines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
5 $(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 ,
10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-

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C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

4. The compound of claim 1 wherein DYE is an aromatic or a heteroaromatic radical derived from rhodamines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 , R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

5. The compound of claim 1 wherein DYE is an aromatic or a heteroaromatic radical derived from porphyrins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and

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steroid receptor binding molecules; L is selected from the group consisting of -
 $(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected
 from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-
 C10 alkyl, C1-C10 polyhydroxyalkyl, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10}
 are independently selected from the group consisting of hydrogen, C1-C10 alkyl,
 and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0
 to 6.

6. The compound of claim 1 wherein DYE is an aromatic or heteroaromatic
 radical derived from benzoporphyrins; E is selected from the group consisting of
 somatostatin receptor binding molecules, heat sensitive bacterioendotoxin
 receptor binding molecules, neurotensin receptor binding molecules, bombesin
 5 receptor binding molecules, cholestekinin receptor binding molecules, and
 steroid receptor binding molecules; L is selected from the group consisting of -
 $(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected
 from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-
 C10 alkyl, C1-C10 polyhydroxyalkyl, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10}
 are independently selected from the group consisting of hydrogen, C1-C10 alkyl,
 and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0
 to 6.

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7. The compound of claim 1 wherein DYE is an aromatic or heteroaromatic radical derived from corrins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
 5 $(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

8. The compound of claim 1 wherein DYE is an aromatic or heteroaromatic radical derived from phenothiazines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
 5 $(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-

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C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

9. The compound of claim 1 wherein DYE is an aromatic or heteroaromatic radical derived from hypocrellins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 , R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

10. The compound of claim 1 wherein DYE is an aromatic or heteroaromatic radical derived from indolenium dyes; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and

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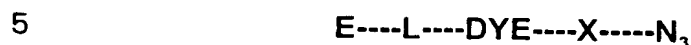
steroid receptor binding molecules; L is selected from the group consisting of -
 $(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected
 from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-
 C10 alkyl, C1-C10 polyhydroxyalkyl, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10}
 are independently selected from the group consisting of hydrogen, C1-C10 alkyl,
 and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0
 to 6.

11. The compound of claim 1 wherein E is associated with a biomolecule
 selected from the group consisting of hormones, amino acids, peptides,
 peptidomimetics, proteins, nucleosides, nucleotides, nucleic acids, enzymes,
 carbohydrates, glycomimetics, lipids, albumins, monoclonal antibodies, polyclonal
 5 antibodies, receptors, inclusion compounds, receptor binding molecules,
 polyaminoacids, polyols, polyamines, polyacids, oligonucleotides, aborols,
 dendrimers, and aptamers.

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12. A method of performing a phototherapeutic procedure which comprises the steps of:

(a) administering to a target tissue in an animal an effective amount of organic azide photosensitizer having the formula



wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes; E is a hydrogen atom or is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules; L is selected from the group consisting of $-(\text{CH}_2)_a-$, $-(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{OCONH}-$, $-\text{OCO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, $-\text{HNNHCO}-$, $-\text{OSO}_2-$, $-\text{NR}^3(\text{CH}_2)_e\text{CONR}^4-$, $-\text{CONR}^5(\text{CH}_2)_f\text{NR}^6\text{CO}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-\text{HNCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, -OH, C1-C10 polyhydroxyalkyl, C1-C10 alkoxyl, C1-C10 alkoxyalkyl, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10} are independently selected from the

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- group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl; and a to l independently range from 0 to 10; and
- 25 (b) exposing said target tissues with the light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

13. The method of claim 12 further comprising the step of allowing said photosensitizer to accumulate in said target tissue.
14. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from cyanines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
 5 $(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; $R^1, R^2,$
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

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15. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from phthalocyanines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin
5 receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
(CH₂)_bCONR¹-, -N(R²)CO(CH₂)_c-, -OCO(CH₂)_d-, -(CH₂)_eCO₂-, -HNCONH-, -
HNCSNH-, and -NR⁷CO(CH₂)_gCONR⁸-; X is either a single bond or is selected
from the group consisting of -(CH₂)_h-, -OCO-, -(CH₂)_iCO-, and -(CH₂)_jOCO-, R¹, R²,
10 R⁷ and R⁸ are independently selected from the group consisting of hydrogen, C1-
C10 alkyl, C1-C10 polyhydroxyalkyl, -(CH₂)_kCO₂H, and -(CH₂)_lNR⁹R¹⁰; R⁹ and R¹⁰
are independently selected from the group consisting of hydrogen, C1-C10 alkyl,
and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0
to 6.

16. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from rhodamines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin
5 receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of -
(CH₂)_bCONR¹-, -N(R²)CO(CH₂)_c-, -OCO(CH₂)_d-, -(CH₂)_eCO₂-, -HNCONH-, -
HNCSNH-, and -NR⁷CO(CH₂)_gCONR⁸-; X is either a single bond or is selected
from the group consisting of -(CH₂)_h-, -OCO-, -(CH₂)_iCO-, and -(CH₂)_jOCO-, R¹, R²,
10 R⁷ and R⁸ are independently selected from the group consisting of hydrogen, C1-

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C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

17. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from porphyrins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 , R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

18. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from benzoporphyrins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and

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steroid receptor binding molecules; L is selected from the group consisting of -
 $(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected
 10 from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 , R^2 ,
 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-
 C10 alkyl, C1-C10 polyhydroxyalkyl, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10}
 are independently selected from the group consisting of hydrogen, C1-C10 alkyl,
 and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0
 to 6.

19. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic
 radical derived from corrins; E is selected from the group consisting of
 somatostatin receptor binding molecules, heat sensitive bacterioendotoxin
 receptor binding molecules, neurotensin receptor binding molecules, bombesin
 5 receptor binding molecules, cholestekinin receptor binding molecules, and
 steroid receptor binding molecules; L is selected from the group consisting of -
 $(\text{CH}_2)_b\text{CONR}^1-$, $-\text{N}(\text{R}^2)\text{CO}(\text{CH}_2)_c-$, $-\text{OCO}(\text{CH}_2)_d-$, $-(\text{CH}_2)_e\text{CO}_2-$, $-\text{HNCONH}-$, $-\text{HNCSNH}-$, and $-\text{NR}^7\text{CO}(\text{CH}_2)_g\text{CONR}^8-$; X is either a single bond or is selected
 from the group consisting of $-(\text{CH}_2)_h-$, $-\text{OCO}-$, $-(\text{CH}_2)_i\text{CO}-$, and $-(\text{CH}_2)_j\text{OCO}-$; R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-
 C10 alkyl, C1-C10 polyhydroxyalkyl, $-(\text{CH}_2)_k\text{CO}_2\text{H}$, and $-(\text{CH}_2)_l\text{NR}^9\text{R}^{10}$; R^9 and R^{10}
 are independently selected from the group consisting of hydrogen, C1-C10 alkyl,
 and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0
 to 6.

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20. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from phenothiazines; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin
 5 receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of - $(CH_2)_bCONR^1$ -, $-N(R^2)CO(CH_2)_c$ -, $-OCO(CH_2)_d$ -, $-(CH_2)_eCO_2$ -, $-HNCONH$ -, $-HNCSNH$ -, and $-NR^7CO(CH_2)_gCONR^8$ -; X is either a single bond or is selected from the group consisting of $-(CH_2)_h$ -, $-OCO$ -, $-(CH_2)_iCO$ -, and $-(CH_2)_jOCO$ -, R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

21. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from hypocrellins; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin
 5 receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of - $(CH_2)_bCONR^1$ -, $-N(R^2)CO(CH_2)_c$ -, $-OCO(CH_2)_d$ -, $-(CH_2)_eCO_2$ -, $-HNCONH$ -, $-HNCSNH$ -, and $-NR^7CO(CH_2)_gCONR^8$ -; X is either a single bond or is selected from the group consisting of $-(CH_2)_h$ -, $-OCO$ -, $-(CH_2)_iCO$ -, and $-(CH_2)_jOCO$ -, R^1 , R^2 ,
 10 R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-

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C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

22. The method of claim 12, wherein DYE is an aromatic or a heteroaromatic radical derived from indolenium dyes; E is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholestekinin receptor binding molecules, and steroid receptor binding molecules; L is selected from the group consisting of $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-HNCONH-$, $-HNCSNH-$, and $-NR^7CO(CH_2)_gCONR^8-$; X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$; R^1 , R^2 , R^7 and R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C10 polyhydroxyalkyl, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$; R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, and C1-C10 polyhydroxyalkyl; and b-e and g-j independently range from 0 to 6.

23. The method of claim 12 wherein E is associated with a biomolecule selected from the group consisting of hormones, amino acids, peptides, peptidomimetics, proteins, nucleosides, nucleotides, nucleic acids, enzymes, carbohydrates, glycomimetics, lipids, albumins, monoclonal antibodies, polyclonal antibodies, receptors, inclusion compounds, receptor binding molecules,

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polyaminoacids, polyols, polyamines, polyacids, oligonucleotides, aborols, dendrimers, and aptamers.

24. The method of claim 23 wherein the effective amount of the organic azide photosensitizer administered to the target tissue is in a range of about 0.1 mg/kg body weight to about 500 mg/kg body weight.

25. The method of claim 24 wherein the effective amount of the organic azide photosensitizer administered to the target tissue is in a range of about 0.5 mg/kg body weight to about 2 mg/kg body weight.

26. The method of claim 12 wherein the organic azide photosensitizer is parenterally administered to the target tissue in a formulation including the organic azide photosensitizer and materials selected from the group consisting of pharmaceutically acceptable buffers, emulsifiers, surfactants, and electrolytes.

27. The method of claim 26 wherein the formulation is parenterally administered to the target tissue in a concentration in a range of about 1 nM to about 0.5 M.

28. The method of claim 12 wherein the organic azide photosensitizer is enterally administered to the target tissue in a formulation including the organic azide photosensitizer and materials selected from the group consisting of buffers, surfactants, emulsifiers, and thixotropic agents.

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29. The method of claim 12 wherein the organic azide photosensitizer is topically administered to the target tissue in a formulation including the organic azide photosensitizer and materials selected from the group consisting of liquid excipients and semisolid excipients.

30. The method of claim 12 wherein the organic azide photosensitizer is administered in a form selected from the group consisting of an aerosol spray, a cream, a gel, and a solution.

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31. A method of performing a phototherapeutic procedure which comprises the steps of:

(a) preparing a homogeneous photosensitizing mixture consisting of two or more Type 1 agents,

- 5 (b) administering said photosensitizing mixture to a target tissue in an animal; and
(c) exposing said target tissues with the light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

32. The method of claim 31, wherein said photosensitizing mixture comprises azides.

33. The method of claim 32, further comprising the step of allowing said photosensitizing mixture to accumulate in said target tissue.

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34. A method of performing a phototherapeutic procedure which comprises the steps of:

- (a) preparing a homogeneous photosensitizing mixture consisting of two or more Type 2 (PDT) agents,
- 5 (b) administering said photosensitizing mixture to a target tissue in an animal; and
- (c) exposing said target tissues with the light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

35. The method of claim 34, wherein said photosensitizing mixture comprises phthalocyanines and porphyrins.

36. The method of claim 35, further comprising the step of allowing said photosensitizing mixture to accumulate in said target tissue

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37. A method of performing a phototherapeutic procedure which comprises the steps of:

- (a) preparing a heterogeneous photosensitizing mixture consisting of one or more Type 1 agents and one or more Type 2 agents,
- 5 (b) administering said photosensitizing mixture to a target tissue in an animal; and
- (c) exposing said target tissues with the light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

38. The method of claim 37, wherein said photosensitizing mixture comprises azides, phthalocyanines and porphyrins.

39. The method of claim 38, further comprising the step of allowing said photosensitizing mixture to accumulate in said target tissue.

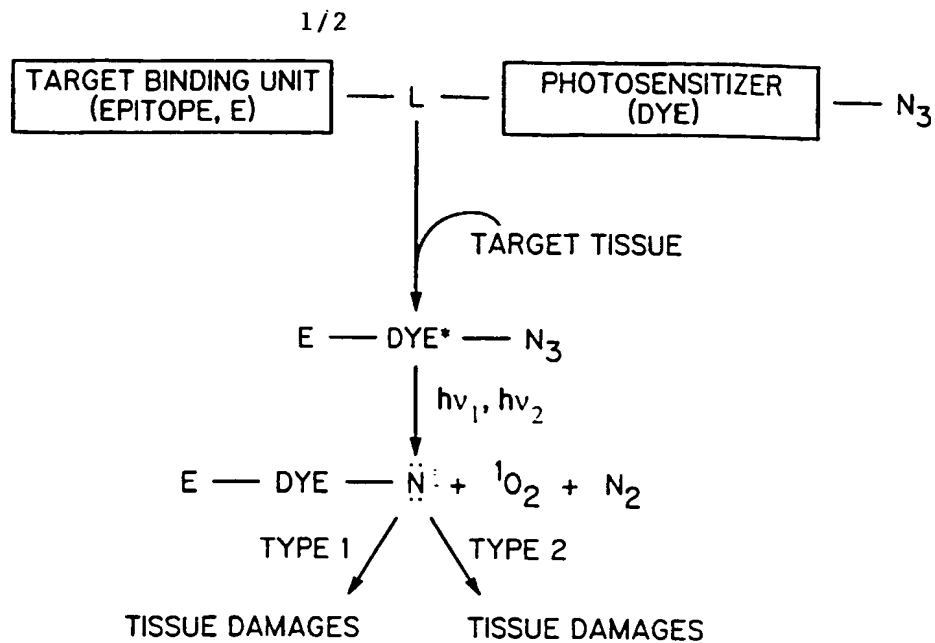


FIG. 1

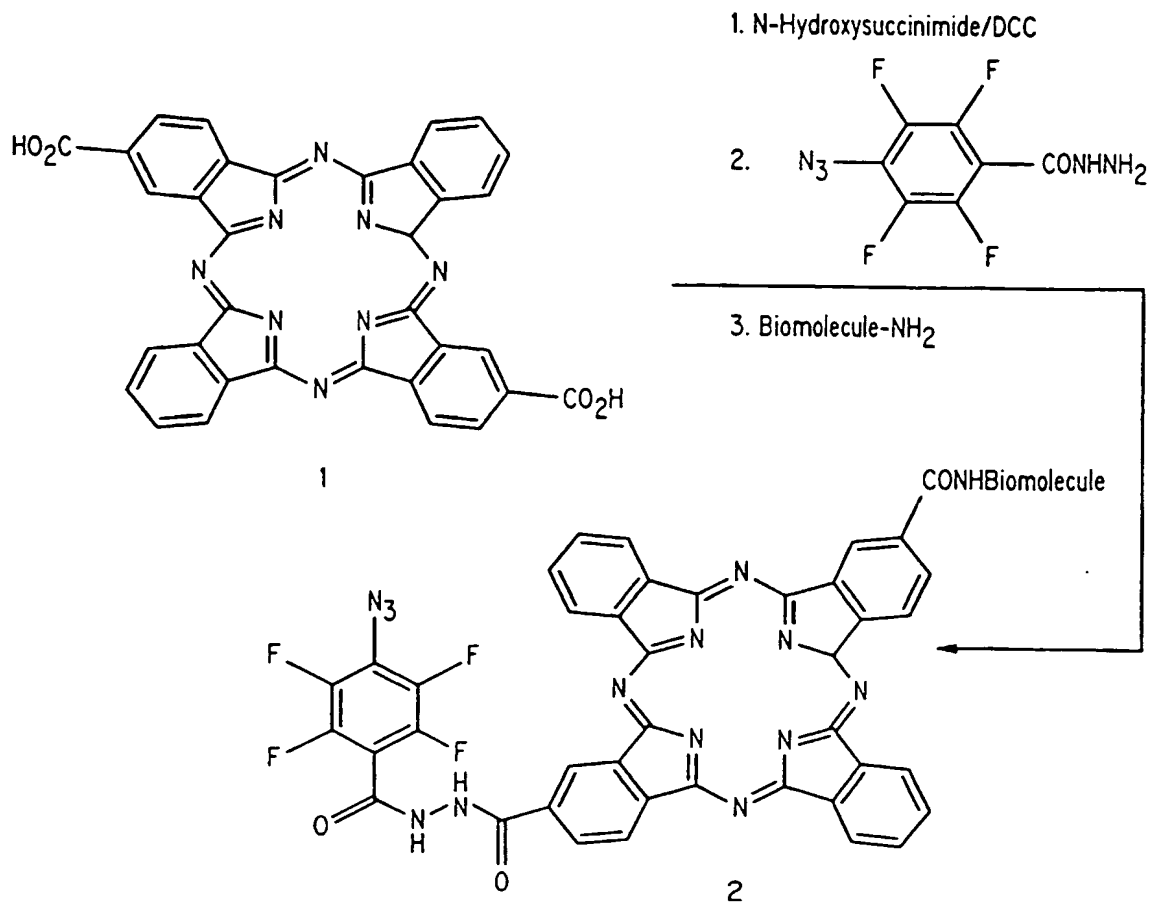


FIG. 2

2/2

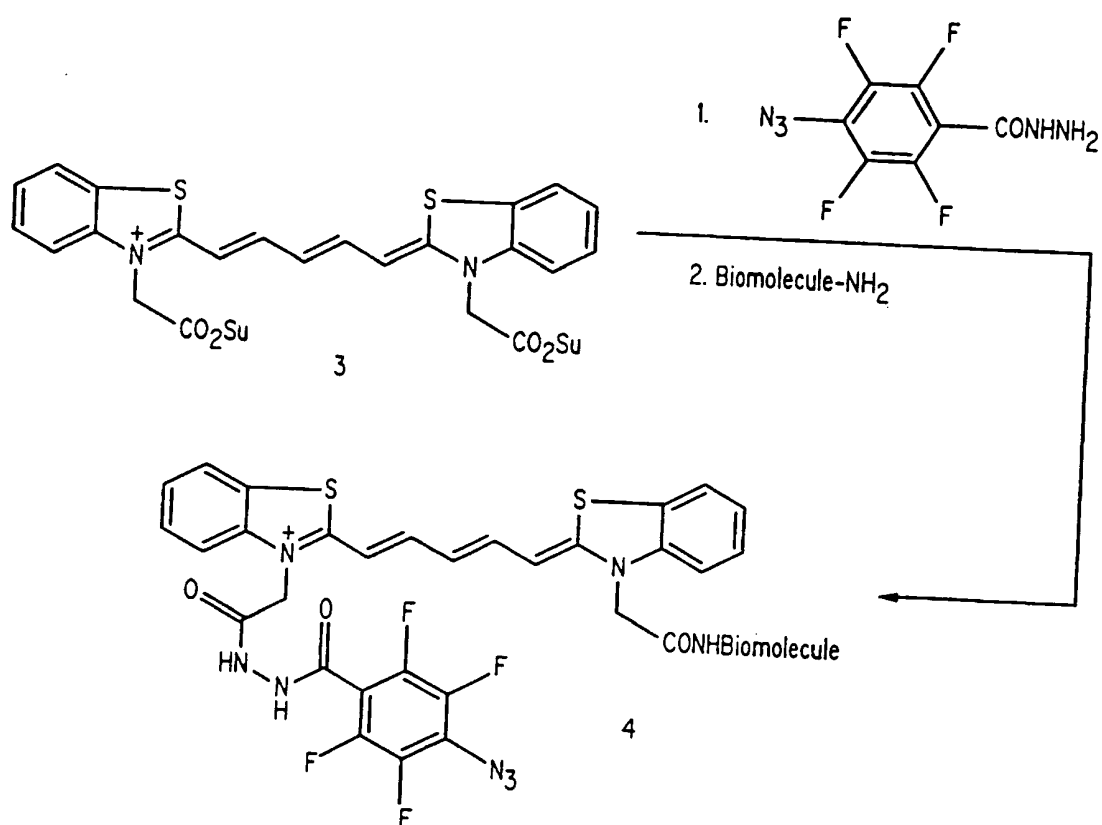


FIG. 3

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(74) Agent: **CHEATHAM, Tim, A.**; Mallinckrodt Inc., 675
McDonnell Boulevard, P.O. Box 5840, St. Louis, MO
63134 (US).

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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
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(71) Applicant (*for all designated States except US*):
MALLINCKRODT, INC. [US/US]; 675 McDonnell
Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **RAJAGOPALAN,**
Raghavan [US/US]; Gliatech, 23420 Commerce Park
Road, Beechwood, OH 44122 (US). **ACHILEFU, Samuel,**
I. [NG/US]; 3424 San Sevilla Court, St. Louis, MO 63044
(US). **BUGA, Joseph, E.** [US/US]; 2916 Kettering Drive,
St. Charles, MO 63303 (US). **DORSHOW, Richard,**
B. [US/US]; 11977 Neihaus Lane, St. Louis, MO 63146
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DYE-AZIDE COMPOUNDS FOR DUAL PHOTOTHERAPY

(57) Abstract: The present invention discloses dye-azide derivatives and their bioconjugates for dual phototherapy of tumors and other lesions. The compounds of the present invention may contain either a mixture of Type 1 and Type 2 agents or a single entity that integrates both units in the same molecules. The compounds are designed to produce both Type 1 and Type 2 phototherapeutic effect at once using dual wavelength light source that will produce singlet oxygen and nitrene at the lesion of interest.

WO 2003/003806 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19187

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 277/64; A61K 33/44; C07K 17/02; C12N 11/02

US CL : 424/94.1, 179.1, 181.1; 548/156; 514/367; 530/391.5, 391.9, 404, 408, 409; 435/6, 177

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/94.1, 179.1, 181.1; 548/156; 514/367; 530/391.5, 391.9, 404, 408, 409; 435/6, 177

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 3,887,379 A (CLECAK et al) 03 June 1975 (03.06.1975), Examples I, III, and IV.	1 ----- 2, 11-14, 23-30
X --- A	US 6,004,536 A (LEUNG et al) 21 December 1999 (21.12.1999), formula of col. 4, line 20; col. 5, lines 45-53; col. 6, lines 10-27, col. 16, lines 14-24.	1 ----- 2, 11-14, 23-30
X --- A	OL'SHEVSKAYA, I. et al. Synthesis and Reactions of Azides of Heterocyclic compounds. III. Cyanine Dyes from azidobenzothiazole and benzimidazole. Khim. Geterotsikl, Soedin. 1974, Vol 5, pages 640-642, especially the structures of page 640.	1 ----- 2, 11-14, 23-30
X --- A	Database JCAPLUS on STN, AN 1984:439814. POCHINOK, V. et al. 'Photochemistry of Azide Group-Containing Dyes in Solution'. Abstract of Ukr. Khim. Zh. (Russ. Ed.) 1984, Vol 50, No 3, pages 296-301, the fourth structure of page 2; all structures of page 4.	1 ----- 2, 11-14, 23-30
A	US 6,077,584 A (HURDITCH) 20 June 2000 (20.06.2000), col. 7, lines 55-63; structures (I) - (III) and (VI).	1, 2, 11-14, 23-30



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:		"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2003 (26.11.2003)	18 DEC 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Mary E. Ceperley Telephone No. (703) 308-1234

INTERNATIONAL SEARCH REPORT

PCT/US02/19187

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 11-174672 A (MITSUBISHI CHEMICAL CORP.) 02 July 1999 (02.07.1999), structures (II), (II-8)-(II-10)	1, 2, 11-14, 23-30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19187

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 2, 11-14, and 23-30

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/19187

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1, 2, 11-14, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a cyanine dye.

Group II, claim(s) 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is an indocyanine dye.

Group III, claim(s) 1, 3, 11-13, 15, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a phthalocyanine dye.

Group IV, claims 1, 4, 11-13, 16, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a rhodamine dye.

Group V, claims 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a phenoxazine dye.

Group VI, claims 1, 8, 11-13, 20, and 23-30 (at least part of each) drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a phenothiazine dye.

Group VII, claims 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a phenoselenazine dye.

Group VIII, claims 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a fluorescein dye.

Group IX, claims 1, 5, 11-13, 17, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a porphyrin dye.

Group X, claims 1, 6, 11-13, 18, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a benzoporphyrin dye.

Group XI, claims 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a squaraine dye.

INTERNATIONAL SEARCH REPORT

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Group XII, claims 1, 7, 11-13, 19, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a corrin.

Group XIII, claims 1, 11-13 and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a croconium dye.

Group XIV, claims 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a azo dye.

Group XV, claims 1, 11-13, and 23-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a methine dye.

Group XVI, claims 1, 10-13, and 22-30 (at least part of each), drawn to compounds and biomolecules associated with the compounds and a method of phototherapy using the compounds wherein the dye is a indolenium dye.

Group XVII, claims 31-33, drawn to a phototherapy method which uses Type I agents.

Group XVIII, claims 34-36, drawn to a phototherapy method which uses Type I agents.

Group XIX, claims 37-39, drawn to a phototherapy method which uses a combination of Type I and Type II agents.

****Note:** Claims 9 and 21 are directed to the use of hypocrellin dyes. Applicants should indicate which of the above groups these dye compounds belong to.

The inventions listed as Groups I-XIX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Each of the above groups is drawn to dye compounds which are different both structurally and functionally from the dyes of the other groups. A reference which would anticipate or render obvious the members of one group would not necessarily render obvious the members of any other group. Further, the compounds of Groups XVII-XIX are not even required to contain an azide moiety.

Continuation of B. FIELDS SEARCHED Item 3:

APS, CAS ONLINE

search terms: cyanine, azide, nitrene, azido, photosensitive, phototherapy, necrosis, apoptosis, photodynamic, singlet oxygen, type I, type II

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